TNFRSF11A gene

TNF receptor superfamily member 11a

Normal Function

The *TNFRSF11A* gene provides instructions for making a protein called receptor activator of NF-κB (RANK). This protein plays an important role in bone remodeling, a normal process in which old bone is broken down and new bone is created to replace it. During bone remodeling, RANK helps direct the formation and function of specialized cells called osteoclasts, which break down bone tissue. RANK is located on the surface of immature osteoclasts, where it receives signals that trigger these cells to mature and become fully functional.

Health Conditions Related to Genetic Changes

osteopetrosis

Paget disease of bone

At least two very similar mutations in the *TNFRSF11A* gene have been found to cause the rare, early-onset form of Paget disease of bone. Both mutations are duplications, which means that they abnormally copy a segment of genetic material within the gene. Each of these mutations results in the production of a RANK protein that contains several extra protein building blocks (amino acids).

Through a mechanism that is not well understood, duplication mutations in the *TNFRSF11A* gene appear to overactivate the chemical signaling pathway that promotes osteoclast formation. The increased signaling stimulates the production of too many osteoclasts and triggers these cells to break down bone abnormally. In people with early-onset Paget disease of bone, affected bone is broken down and replaced much faster than usual. When the new bone tissue grows, it is weaker and less organized than normal bone. These problems with bone remodeling cause certain bones to become unusually large, misshapen, and easily broken (fractured).

other disorders

Mutations in the *TNFRSF11A* gene are responsible for several other rare bone diseases, including two very similar disorders called familial expansile osteolysis (FEO) and expansile skeletal hyperphosphatasia (ESH). These disorders have signs and symptoms that overlap with those of early-onset Paget disease of bone. In fact, some researchers believe that FEO, ESH, and early-onset Paget disease of bone actually may be slightly different forms of a single condition. FEO and ESH both

appear early in life and are characterized by skeletal abnormalities, tooth loss, and progressive hearing loss.

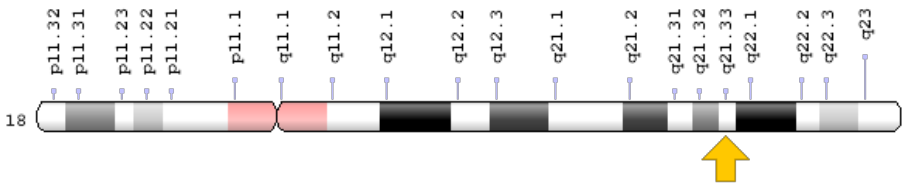
Like early-onset Paget disease of bone, FEO and ESH result from duplication mutations in the *TNFRSF11A* gene. Studies suggest that these mutations overactivate RANK, leading it to stimulate the production of too many osteoclasts and trigger these cells to break down bone abnormally. The resulting imbalance in bone remodeling causes the major features of these disorders. It is unclear why duplication mutations in the *TNFRSF11A* gene can cause several different bone diseases.

TNFRSF11A gene mutations also cause a bone disease called autosomal recessive osteopetrosis (ARO). This disorder appears in infancy and is characterized by abnormally dense bones. The increased bone density leads to a variety of complications, including an increased risk of fractures, vision impairment, hearing loss, and problems with the immune system related to defective bone marrow. Mutations in the *TNFRSF11A* gene appear to be a very rare cause of ARO; fewer than 10 mutations have been found in affected individuals. Most of these mutations change single amino acids in the RANK protein, which prevents it from receiving signals on the surface of immature osteoclasts. As a result, people with this condition have a total absence of mature, functional osteoclasts. Without these specialized cells to break down bone tissue, excess bone is formed throughout the skeleton.

Chromosomal Location

Cytogenetic Location: 18q21.33, which is the long (q) arm of chromosome 18 at position 21.33

Molecular Location: base pairs 62,325,287 to 62,388,096 on chromosome 18 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- CD265
- FEO
- ODFR

- OFE
- OPTB7
- osteoclast differentiation factor receptor
- OSTS
- PDB2
- RANK
- receptor activator of NF-kappa-B
- receptor activator of nuclear factor-kappa B
- TNR11_HUMAN
- TRANCER
- tumor necrosis factor receptor superfamily member 11a
- tumor necrosis factor receptor superfamily member 11a, NFKB activator
- tumor necrosis factor receptor superfamily, member 11a
- tumor necrosis factor receptor superfamily, member 11a, activator of NFKB
- tumor necrosis factor receptor superfamily, member 11a, NFKB activator

Additional Information & Resources

Educational Resources

- Molecular Biology of the Cell (fourth edition, 2002): Bone Is Continually Remodeled by the Cells Within It
  https://www.ncbi.nlm.nih.gov/books/NBK26889/#A4187

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28TNFRSF11A%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- FAMILIAL EXPANSILE OSTEOLYSIS
  http://omim.org/entry/174810
- OSTEOPETROSIS, AUTOSOMAL RECESSIVE 7
  http://omim.org/entry/612301
- TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 11A
  http://omim.org/entry/603499

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_TNFRSF11A.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=TNFRSF11A%5Bgene%5D
- HGNC Gene Family: CD molecules
  http://www.genenames.org/cgi-bin/genefamilies/set/471
- HGNC Gene Family: Tumor necrosis factor receptor superfamily
  http://www.genenames.org/cgi-bin/genefamilies/set/782
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=11908
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/8792
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https://ghr.nlm.nih.gov/gene/TNFRSF11A

Reviewed: February 2010
Published: March 21, 2017

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